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MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
HUYNH, PHUONG N	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/627,631	ACHEN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-27 and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-27 and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/12/06 has been entered.

2. Claims 8-27 and 36-44 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 8-27 and 36-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 14, 18, 23, 36 and 40 are incomplete for missing steps for detecting *unprocessed* VEGF-D polypeptide in cells from a sample obtained from an organism suspected of being in neoplastic state. In order to detect unprocessed versus processed VEGF-D, the size of VEGF-D in the sample must be determined. Histochemistry does not detect the size of the VEGF-D fragment. Further, it is noted that the antibodies 2F8, 5F12 and 4A5 (renamed as VD1, VD2, and VD3, respectively) bind to the homology domain in *both* the processed and unprocessed VEGF-D. As such, the antibody is not specific for just the full-length unprocessed VEGF-D. It is not clear one of ordinary skill in the art could screen for any neoplastic disease by detecting the presence, quantity or distribution of *unprocessed VEGF-D* in cells given the unspecific antibodies. Finally, the claimed method as recited in claims 8, 14, 18, 23, 36 and 40 missing the control, which enables one of ordinary skill in the art to compare to and arrive at the conclusion that the level of unprocessed VEGF-D is increased in cells obtained from an organism suspect of being in a neosplastic disease. The remaining claims are rejected for depending from said rejected claims 8, 14, 18, 23, 36 and 40.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 8-11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/07832 publication (published February 26, 1998; PTO 1449).

The WO 98/07832 publication teaches a method for diagnosing or screening for cancer associated VEGF-D by obtaining a sample such as biopsy specimens from patient with cancer where tumor produce VEGF-D in order to provide for angiogenesis (see page 10, lines 21-29, page 12, lines 6-14, page 14, lines 19-20, in particular), exposing said sample to a composition comprising an antibody such as polyclonal or monoclonal antibody that specifically binds to the full-length (unprocessed) human VEGF-D comprising SEQ ID NO: 5 and detecting the presence or quantitation of VEGF-D in cancer biopsy specimens is useful as an indicator of future metastatic risk (see page 9, lines 29 through page 10, lines 1-29, page 26, line 6-8, claims 58-59, 30-32, 19-20 and 16 of the WO 98/07832 publication, page 35, lines 9-20, abstract, in particular). The reference monoclonal antibody includes a detectable label such as supermagnetic, paramagnetic, radioactive agent, biotin/avidin for diagnostic purpose (see page 10, line 10-20, claim 32 of the WO 98/07832 publication, in particular). The recitation of an increase level of unprocessed VEGF-D polypeptide is an inherent characteristic of cancer. Thus, the reference teachings anticipate the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 8 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07832 publication (published February 26, 1998; PTO 1449) in view of WO 99/33485 publication (of record, July 8, 1999, PTO 1449).

The teachings of WO 98/07832 publication have been discussed supra.

The claimed invention as recited in claim 12 differs from the teachings of the reference only in that the method wherein the neoplastic disease is melanoma.

The WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk wherein the reference method steps comprise: (1) obtaining a sample such as a biopsy specimen from patient with melanoma (See page 20, lines 1-10, page 32 at line 18, in particular), (2) exposing the biopsy specimen to a composition comprising an antibody such as monoclonal antibody such as 2F8, 5F12, 4A5 and 4E10 that bind specifically to processed VEGF-D for immunohistochemistry analysis (See page 32, lines 18-19, in particular), (3) washing the sample (see page 33, line 19, in particular) and (4) assessing for the presence or increase in the VEGF-D expression in or around a potential neoplastic growth (See pages 33-35, Figs 7A-E, in particular). The reference teaches VEGF-D monoclonal antibodies detected VEGF-D in melanoma cells in both clinical samples, and the detection of VEGF-D indicates these tumor cells are most likely producing said VEGF-D (See page 35, lines 13-15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screening for neoplastic disease such as melanoma expressing VEGF-D as taught by the WO 99/33485 publication using an antibody that binds to the unprocessed full-length VEGF-D polypeptide as taught by the WO 98/07832 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 98/07832 publication teaches detecting the presence or quantitation of VEGF-D in cancer biopsy specimens is useful as an indicator of future metastatic risk (see page 9, lines 29 through page 10, lines 1-29, page 26, line 6-8, claims 58-59, 30-32, 19-20 and 16 of the WO 98/07832

publication, page 35, lines 9-20, abstract, in particular). Further, t is noted that the reference antibodies 2F8, 5F12 and 4A5 in the method as taught by the WO 99/33485 publication are the same antibodies 2F8, 5F12 and 4A5 of instant application (now renamed as VD1, VD2, and VD3, respectively) would obviously bind to the unprocessed VEGF-D as well since the homology to which the antibodies in the fully processed and unprocessed VEGF-D.

10. Claims 14-21 and 36-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/33485 publication (of record, July 8, 1999, PTO 1449) in view of WO 98/07832 publication (published February 26, 1998; PTO 1449).

The WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk wherein the reference method steps comprise: (1) obtaining a sample such as a biopsy specimen from patient with melanoma (See page 20, lines 1-10, page 32 at line 18, in particular), (2) exposing the biopsy specimen to a composition comprising an antibody such as monoclonal antibody such as 2F8, 5F12, 4A5 and 4E10 that bind specifically to processed VEGF-D for immunohistochemistry analysis (See page 32, lines 18-19, in particular), (3) washing the sample (see page 33, line 19, in particular) and (4) assessing for the presence or increase in the VEGF-D expression in or around a potential neoplastic growth (See pages 33-35, Figs 7A-E, in particular). The reference teaches VEGF-D monoclonal antibodies detected VEGF-D in melanoma cells in both clinical samples, and the detection of VEGF-D indicates these tumor cells are most likely producing said VEGF-D (See page 35, lines 13-15, in particular). The reference VEGF-D antibody binds to VEGF homology domain of VEGF-D such as VEGF-D having a deletion at the N and C terminals (VEGF-DΔNΔC) (See page 29, 15-23, page 31, line 3, Fig 1 in particular) and the reference antibody includes a detectable label such as FITC (See page 20, lines 11-20, claims 28-30 of WO 99/33485 publication, in particular). The WO 99/33485 publication teaches that VEGF-D is detected on the endothelial cells of blood vessels in the vicinity of tumor cells but not detected on more distant vessels (non tumor vessels) (See page 35, lines 14-17, in particular). The recitation of micro-metastasis in claim 40 is within the teachings of WO 99/33485 publication because the WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk. The WO 99/33485 publication teaches VEGF-D binds to both VEGFR-2 and VEGFR-3 (see page 45, pages 13-14, in particular) and antibody to VEGFR-2 and VEGFR-3 may also be used since VEGF-D, VEGFR-2 and

VEGFR-3 are expressed on proliferating vascular and lymphatic endothelial cells (see page 15, lines 14-15, page 16, line 4-5, in particular).

The claimed invention differs from the teachings of the reference only in that the method of screening for neoplastic disease using antibody that specifically binds to unprocessed (full-length) VEGF-D polypeptide instead of antibody that binds to processed VEGF-D containing the homology domain.

The WO 98/07832 publication teaches a method for diagnosing or screening for cancer associated VEGF-D obtaining a sample such as biopsy specimens from patient with cancer where tumor produce VEGF-D in order to provide for angiogenesis (see page 10, lines 21-29, page 12, lines 6-14, page 14, lines 19-20, in particular), exposing said sample to a composition comprising an antibody such as polyclonal or monoclonal antibody that specifically binds to the full-length (unprocessed) human VEGF-D comprising SEQ ID NO: 5 and detecting the presence or quantitation of VEGF-D in cancer biopsy specimens is useful as an indicator of future metastatic risk (see page 9, lines 29 through page 10, lines 1-29, page 26, line 6-8, claims 58-59, 30-32, 19-20 and 16 of the WO 98/07832 publication, page 35, lines 9-20, abstract, in particular). The reference monoclonal antibody includes a detectable label such as supermagnetic, paramagnetic, radioactive agent, biotin/avidin for diagnostic purpose (see page 10, line 10-20, claim 32 of the WO 98/07832 publication, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody such as 2F8, 5F12, 4A5 and 4E10 that binds to processed form of VEGF-D in the method of screening for neoplastic disease as taught by the WO 99/33485 publication for the polyclonal or monoclonal antibody that binds to the unprocessed full-length VEGF-D as taught by the WO 98/07832 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 98/07832 publication teaches antibody to the full-length or fragment of VEGF-D is useful for diagnosing or screening for cancer associated VEGF-D and detecting the presence or quantitation of VEGF-D in cancer biopsy specimens is useful as an indicator of future metastatic risk (see page 9, lines 29 through page 10, lines 1-29, page 26, line 6-8, claims 58-59, 30-32, 19-20 and 16 of the WO 98/07832 publication, page 35, lines 9-20, abstract, in particular). It would

have been obvious that the level of VEGF-D polypeptide in tumor cells increases given that the levels of other VEGFs are also increase in tumor as taught by the WO 99/33485 publication.

Applicants' arguments filed 10/12/06 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended, the WO/9933485 does not teach the use of an antibody that specifically binds to unprocessed (full length) VEGF-D. Achen et al reference (Eur J Biochem 267: 2505-2515, May 2000) was not published until after the earliest priority date of the present application. Instant application claims priority to provisional application 60/186,361, filed March 2, 2000. More importantly, tumors expressing the full-length VEGF-D had more blood vessels and lymphatic vessels than tumors that did not express VEGF-D.

In response, the argument with respect to the Achen et al is moot since said reference has been dropped. Although the WO/9933485 does not teach the use of an antibody that specifically binds to unprocessed (full length) VEGF-D, the WO 98/07832 publication (published February 26, 1998; PTO 1449) teaches antibody such as polyclonal or monoclonal antibody to the full-length unprocessed VEGF-D for a method of diagnosing or screening for cancer associated VEGF-D. The reference method comprises obtaining a sample such as biopsy specimens from patient with cancer where tumor produce VEGF-D in order to provide for angiogenesis (see page 10, lines 21-29, page 12, lines 6-14, page 14, lines 19-20, in particular), exposing said sample to a composition comprising an antibody such as polyclonal or monoclonal antibody that specifically binds to the full-length (unprocessed) human VEGF-D comprising SEQ ID NO: 5 and detecting the presence or quantitation of VEGF-D in cancer biopsy specimens which is useful as an indicator of future metastatic risk (see page 9, lines 29 through page 10, lines 1-29, page 26, line 6-8, claims 58-59, 30-32, 19-20 and 16 of the WO 98/07832 publication, page 35, lines 9-20, abstract, in particular). Finally, it is noted that the antibodies such as 4A5, 5F12, and 2F8 (renamed as VD1, VD2 and VD3, respectively) in the instant specification at page 48 are the same antibodies 2F8, 5F12, 4A5 that binds VEGF-D as taught the WO 99/33485 publication. The instant specification discloses the antibodies 2F8, 5F12 and 4A5 are produced by immunizing mice with human VEGF-D from residues 93-201 (see instant specification at page 41). The WO/9933485 publication teaches monoclonal antibodies 2F8, 5F12 and 4A5 are produced by immunizing mice with human VEGF-D from residues 93-201 (see page 29, lines 15-22, in particular). The reference antibodies 2F8, 5F12 and 4A5 obviously cross react with the full-length unprocessed VEGF-D given the long stretch of identical amino acids residues 93-201 of human VEGF-D. Since the Patent Office does

not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibodies are different from the antibodies for the claimed method. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

11. Claims 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/33485 publication (of record, July 8, 1999, PTO 1449) in view of WO 98/07832 publication (published February 26, 1998; PTO 1449) as applied to claims 14-21 and 36-44 mentioned above and further in view of Achen *et al* (of record, Proc. Nat. Acad. Sci USA 95: 548-553, January 1998; PTO 1449) and Valtola *et al* (of record, American J of Pathology 154(5): 1381-1390, May 1999; PTO 1449) or Salven *et al* (of record, Am J Pathol 153(1): 103-8, July 1998; PTO 1449) or Tsurusaki *et al* (Br J Cancer 80(1-2): 309-13, April 1999; PTO 1449).

The combined teachings of the WO 99/33485 publication and WO 98/07832 publication have been discussed supra.

The claimed invention as recited in claim 22 differs from the combined teachings of the references only in that the method further comprises exposing the sample to a second antibody that binds to at least one of VEGFR-2 and VEGFR-3.

The claimed invention as recited in claim 27 differs from the combined teachings of the references only in that the method further comprises exposing the sample to a second antibody that binds to VEGFR-3.

Achen *et al* teach human VEGF-D is a ligand for VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4) and VEGF-D is most closely related to VEGF-C (See Abstract, Fig 1, page 550, column 2, bridging page 551 column 2, in particular). Achen *et al* further teach VEGF-C regulates angiogenesis of the lymphatic vasculature because VEGFR-3 is strongly expressed by the lymphatic endothelium while VEGFR-2 is expressed in vascular endothelial cells (See page 553, column 1, first two full paragraph, in particular). Achen *et al* teach VEGF-D and VEGF-C exist at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular).

Valtola *et al* teach that VEGF-C and VEGFR-3 are associated with angiogenesis in breast cancer (See entire document, in particular). Valtola *et al* teach VEGFR-3 is expressed weakly in the blood vessels of normal breast tissue (see page 1384, column 2, first paragraph, in particular) while intraductal carcinomas is stained positive for VEGFR-3, especially in invasive breast

carcinoma as detected by antibody that binds specifically to VEGF-C and VEGFR-3 (See Fig 1, page 1384, column 2, VEGFR-3 positive vessels intraductal carcinomas, in particular).

Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, squamous cell carcinoma, and melanoma (See page 105, Table 1, in particular). Salven *et al* further teach some tumor such as ductal breast carcinomas and adenocarcinomas do not express any of the known VEGFs, suggesting in these tumors, other angiogenic stimuli such as VEGF-D may be providing the stimuli in these cases (See page 106, column 2, Note added in proof, in particular).

Tsurusaki *et al* teach lymph node dissemination is a major prognostic factor in human cancer. VEGF-C in prostatic carcinoma is significantly higher in lymph node-positive group than in lymph node-negative group. In addition, the number of VEGFR-3-positive vessels is increased in stroma surrounding VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen for breast ductal carcinoma as taught by Valtola *et al* or breast carcinoma, squamous cell carcinoma, and melanoma as taught by Salven et al or metastatic carcinoma as taught by Tsurusaki using any of the monoclonal antibody that binds specifically to the unprocessed VEGF-D as taught by Achen for a method for screening for a neoplastic disease as taught by the WO 99/33485 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach VEGF-D and VEGF-C exists at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular). Valtola *et al* teach VEGF-C and VEGFR-3 are associated with angiogenesis in ductal carcinoma (See entire document, in particular). Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, and squamous cell carcinoma. Tsurusaki *et al* teach the number of VEGFR-3-positive vessels is increased in stroma surrounding the VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular). Claims 22 and 27 are included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to detect VEGFR-2 and VEGFR-3 using antibody that binds to VEGFR-2 and VEGFR-3 because the WO 99/33485 publication teaches VEGF-D binds to both

VEGFR-2 and VEGFR-3 (see page 45, pages 13-14, in particular) and antibody to VEGFR-2 and VEGFR-3 may also be used since VEGF-D, VEGFR-2 and VEGFR-3 are expressed on proliferating vascular and lymphatic endothelial cells (see page 15, lines 14-15, page 16, line 4-5, 10627631in particular).

Applicants' arguments filed 10/12/06 have been fully considered but are not found persuasive.

Applicants' position is that without Achen et al the combination of references does not teach specific assaying of unprocessed VEGF-D level. Further, the Office Action relies on Achen et al to provide the motivation that one of ordinary skill in the art need to combine the references.

In response, the argument with respect to the Achen et al is moot since said reference has been dropped. Although the WO/9933485 does not teach the use of an antibody that specifically binds to unprocessed (full length) VEGF-D, the WO 98/07832 publication (published February 26, 1998; PTO 1449) teaches antibody such as polyclonal or monoclonal antibody to the full-length unprocessed VEGF-D for a method of diagnosing or screening for cancer associated VEGF-D. The reference method comprises obtaining a sample such as biopsy specimens from patient with cancer where tumor produce VEGF-D in order to provide for angiogenesis (see page 10, lines 21-29, page 12, lines 6-14, page 14, lines 19-20, in particular), exposing said sample to a composition comprising an antibody such as polyclonal or monoclonal antibody that specifically binds to the full-length (unprocessed) human VEGF-D comprising SEQ ID NO: 5 and detecting the presence or quantitation of VEGF-D in cancer biopsy specimens which is useful as an indicator of future metastatic risk (see page 9, lines 29 through page 10, lines 1-29, page 26, line 6-8, claims 58-59, 30-32, 19-20 and 16 of the WO 98/07832 publication, page 35, lines 9-20, abstract, in particular).

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 8-11, 13-27 and 36-40, and 42-44 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,730,489 (issued May 4, 2004; PTO 892). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

Claims 8-27 and 36-44 of instant application are interpreted as a method for detecting the presence of VEGF-D polypeptide using antibody that binds to VEGF-D polypeptide in a biological sample. This is because the independent claims 8, 14, 18, 23, 36 and 40 are incomplete for missing steps as how to detect *unprocessed* VEGF-D polypeptide in cells from a sample obtained from an organism suspected of being in neoplastic state. In order to detect unprocessed versus processed VEGF-D, the size of VEGF-D in the sample must be determined. Histochemistry does not detect the size of the VEGF-D fragment. Further, it is noted that the antibodies 2F8, 5F12 and 4A5 (renamed as VD1, VD2, and VD3, respectively) bind to the homology domain in *both* the processed and unprocessed VEGF-D. As such, the antibody is not specific for just the full-length unprocessed VEGF-D. It is not clear one of ordinary skill in the art could screen for any neoplastic disease by detecting the presence, quantity or distribution of *unprocessed VEGF-D* in cells given the unspecific antibodies. Finally, the claimed method as recited in claims 8, 14, 18, 23, 36 and 40 missing the control, which enabled one of ordinary skill in the art to compare to and arrive at the conclusion that the level of unprocessed VEGF-D is increased in cells obtained from an organism suspect of being in a neoclassic disease.

Claim 1 of the '489 patent recites a method of detecting VEGF-D in biological sample, comprising the step of contacting the sample with an antibody or an antibody labeled with a

detectable label which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO:1, wherein said antibody is selected from the group consisting of a monoclonal antibody of 2F8 (ATCC No. PTA-3653), 4A5 (ATCC No. HB-12698), 4E10 (ATCC No. PTA-3652, and 5F12 (ATCC No. PTA-3651), or a F(ab').sub.2, F(ab'), or F(ab) fragment thereof, or a chimeric antibody thereof or a humanized antibody thereof, and detecting the occurrence of binding of said antibody to VEGF-D, species.

Claim 2 of the '489 patent recites a method of detecting VEGF-D in biological sample, comprising the step of contacting the sample with an antibody or an antibody labeled with a detectable label which interferes with an activity of VEGF-D mediated by a VEGF receptor-2 or VEGF receptor-3, wherein said antibody is selected from the group consisting of a monoclonal antibody of 2F8 (ATCC No. PTA-3653), 4A5 (ATCC No. HB-12698), 4E10 (ATCC No. PTA-3652, and 5F12 (ATCC No. PTA-3651), or a F(ab').sub.2, F(ab'), or F(ab) fragment thereof, or a chimeric antibody thereof or a humanized antibody thereof, and detecting the occurrence of binding of said antibody to VEGF-D, species. The '489 patent further teaches diagnosing cancer by means of detecting binding involving the antibody and/or extent of binding is detected by means of a detectable label, or indirectly by means of a second antibody wherein the secondary antibody is coupled to a detectable label and then either an unlabeled primary antibody or VEGF-D is substrate-bound so that the VEGF-D/primary antibody interaction can be established by determining the amount of label bound to the substrate following binding between the primary antibody and VEGF-D and the subsequent binding of the labeled secondary antibody to the primary antibody. The binding of first and second antibody involves the step of washing in between known to one skilled in the art. The species of antibodies in the method of detecting VEGF-D in a biological sample of the issued patent anticipates the genus antibody in the method of detecting VEGF-D of instant that binds to VEGF-D polypeptide of instant application. The issuance of a patent to instant application would include the species of the issued patent.

14. Claims 12 and 41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,730,489 (issued May 4, 2004; PTO 892) in view of Achen *et al* (of record, Proc. Nat. Acad. Sci USA 95: 548-553, January 1998; PTO 1449) and Valtola *et al* (of record, American J of Pathology 154(5): 1381-1390, May 1999; PTO 1449) or Salven *et al* (of record, Am J Pathol 153(1): 103-8, July 1998; PTO 1449) or Tsurusaki *et al* (Br J Cancer 80(1-2): 309-13, April 1999; PTO 1449).

The teachings of the '489 patent have been discussed supra.

The invention in claim 12 differs from the teachings of the '489 patent only in that the method wherein the neoplastic disease is selected form the group consisting of malignant melanoma, breast ductal carcinoma, squamous cell carcinoma, prostate cancer, and endometrial cancer.

The invention in claim 41 differs from the teachings of the '489 patent only in that the method wherein the sample is a lymph node from tissue surrounding neoplastic growth.

Achen *et al* teach human VEGF-D is a ligand for VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4) and VEGF-D is most closely related to VEGF-C (See Abstract, Fig 1, page 550, column 2, bridging page 551 column 2, in particular). Achen *et al* further teach VEGF-C regulates angiogenesis of the lymphatic vasculature because VEGFR-3 is strongly expressed by the lymphatic endothelium while VEGFR-2 is expressed in vascular endothelial cells (See page 553, column 1, first two full paragraph, in particular). Achen *et al* teach VEGF-D and VEGF-C exist at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular).

Valtola *et al* teach that VEGF-C and VEGFR-3 are associated with angiogenesis in breast cancer (See entire document, in particular). Valtola *et al* teach VEGFR-3 is expressed weakly in the blood vessels of normal breast tissue (see page 1384, column 2, first paragraph, in particular) while intraductal carcinomas is stained positive for VEGFR-3, especially in invasive breast carcinoma as detected by antibody that binds specifically to VEGF-C and VEGFR-3 (See Fig 1, page 1384, column 2, VEGFR-3 positive vessels intraductal carcinomas, in particular).

Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, squamous cell carcinoma, and melanoma (See page 105, Table 1, in particular). Salven *et al* further teach some tumor such as ductal breast carcinomas and adenocarcinomas do not express any of the known VEGFs, suggesting in these tumors, other angiogenic stimuli such as VEGF-D may be providing the stimuli in these cases (See page 106, column 2, Note added in proof, in particular).

Tsurusaki *et al* teach lymph node dissemination is a major prognostic factor in human cancer. VEGF-C in prostates carcinoma is significantly higher in lymph node-positive group than in lymph node-negative group. In addition, the number of VEGFR-3-positive vessels is increased in stroma surrounding VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen for breast ductal carcinoma as taught by Valtola *et al* or breast carcinoma, squamous cell carcinoma, and melanoma as taught by Salven et al or metastatic carcinoma via the lymph node dissemination as taught by Tsurusaki using sample from the lymph node as taught by Tsurasaki et al for a method for screening for a neoplastic disease by detecting VEGF-D as taught by Achen and the '489 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach VEGF-D and VEGF-C exists at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular). Valtola *et al* teach VEGF-C and VEGFR-3 are associated with angiogenesis in ductal carcinoma (See entire document, in particular). Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, and squamous cell carcinoma. Tsurusaki *et al* teach the number of VEGFR-3-positive vessels is increased in stroma surrounding the VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
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